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| EXAMINER | |
|---|---|
| NEGIN, RUSSELL SCOTT | |
| **ART UNIT** | **PAPER NUMBER** |
| 1631 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/923,870 | PALSSON, BERNHARD | |
| | Examiner | Art Unit | |
| | RUSSELL S. NEGIN | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *49-52,56-60 and 64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-52,56-60 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Comments*

Applicants' amendments and request for reconsideration in the communication filed on 24 March 2007 are acknowledged and the amendments are entered.

Claims 49-52, 56-60, and 64 are pending and examined in the instant Office action.

### *Withdrawn Objections/Rejections*

The objection to claim 57 is withdrawn in view of amendments filed to the instant claim on 24 March 2008.

The rejections of claims 49-52, 56-60, and 64 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of amendments filed to the set of claims on 24 March 2008.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

<u>The following rejection is reiterated from the previous Office action:</u>

35 U.S.C. 103 Rejection #1:

Claims 49-52 and 56-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pramanik et al. [Biotechnology and Bioengineering, volume 56, 1997, pages 398-421] in view of Blattner et al. [Science, volume 277, 1997, pages 1453-1469].

Claim 49 is drawn to a method performed in a computer of simulating a metabolic capability of an in silico strain of a microbe, comprising:

--obtaining a plurality of DNA sequences comprising most of the metabolic genes in a genome, to produce an in silico representation of a microbe;

--determining open reading frames of genes in said plurality of DNA sequences;

--assigning a function to proteins encoded by said open reading frames by determining the homology of said open reading frames to gene sequences encoding proteins of known function;

--determining which of said open reading frames correspond to metabolic genes by determining if the assigned function of said proteins is involved in cellular metabolism;

--determining substrates, products, and stoichiometry of the reaction for each of the gene products of said metabolic genes;

--producing a genome specific stoichiometric matrix of said microbe produced from said substrates, products and stoichiometry;

--determining a metabolic demand corresponding to a biomass composition of said microbe;

--calculating uptake rates of metabolites of said microbe;

--combining said metabolic demands and said uptake rates with said stoichiometric matrix to produce an in silico representation of said microbe;

--incorporating a general linear programming problem to introduce an in silico strain of said microbe;

--performing a flux balance analysis on said in silico strain, and

--providing a visual output to a user of said analysis that simulated a metabolic capability of said strain.

Claim 57 is drawn to a method performed in a computer for simulating a metabolic capability of an in silico strain of a microbe, comprising;

a) providing a nucleotide sequence of a metabolic gene in the microbe;

b) determining substrates, products and stoichiometry of the reaction for the gene product of said metabolic gene;

c) repeating steps a) and b) for most metabolic genes of said microbe to provide an in silico representation;

d) producing a genome specific stoichiometric matrix produced from said substrates, products and stoichiometry of the metabolic gene products in said microbe;

e) determining a metabolic demand corresponding to a biomass composition of said microbe;

f) calculating uptake rates of metabolites of said microbe;

g) combining said metabolic demands and said uptake rates with said stoichiometric matrix to produce an in silico representation of said microbe;

h) incorporating a general linear programming problem to produce an in silico strain of said microbe;

i) performing a flux balance analysis on said in silico strain, and

j) providing a visual output to a user of said analysis that simulated a metabolic capability of said strain.

Claims 50 and 58 are further limiting wherein the microbe is question is E. coli.

Claims 51 and 59 are further limiting wherein cellular metabolism comprises carbohydrate assimilation and nucleotide metabolism.

Claims 52 and 60 are further limiting wherein the assigning function comprises performing BLAST.

The study of Pramanik et al. investigates the stoichiometric model of E. coli metabolism, as stated in the abstract:

> A stoichiometric model of metabolism was developed to describe the balance of metabolic reactions during steady state growth of Escherichia coli on glucose (or metabolic intermediates) and mineral salts. The model incorporates 153 reversible and 147 irreversible reactions and 289 metabolites from several metabolic data bases…

Consequently, Pramanik et al. studies many metabolic reactions that take place within E. coli (i.e. see the list in Appendix A on pages 411-417). Equations 1 and 2 on page 399 denote the flux model metabolism via a mass balance on E. coli wherein the matrix S is a matrix of stoichiometric coefficients relevant to the equations.

Table VII on page 405 of Pramanik et al. lists the upper and lower bounds of metabolite uptake and secretion, and the text under this table describes sensitivity of each type of metabolism (i.e. aerobic or anaerobic) due to biomass composition. This

biomass and energy requirement (i.e. demand) is elaborated further under "Biomass and energy requirements" in column 2 on page 399 of Pramanik et al.

Again, equations 1 and 2 on page 399 of Pramanik et al. represent a mass balance on the metabolites of E. coli which combines the metabolic demands, uptake rates and the stoichiometric matrix to produce an in silico representation of functions of said microbe.

Page 403 of Pramanik et al., under "Sensitivity Analysis," lists a general linear programming algorithm for solving equations 1 and 2 on page 399 of Pramanik et al.

Figure 3 on page 406 of Pramanik et al. illustrates a flux balance analysis on the in silico strain of E. coli and provides visual output to a user that simulates a metabolic capability of the strain.

However, Pramanik et al. does not teach obtaining a plurality of DNA sequences comprising most of the metabolic genes in an genome, determining open reading frames of these genes, assigning functions to the proteins encoded by the open reading frames, and determining which of said open reading frames correspond to metabolic genes.

The study of Blattner et al. maps the complete genome sequence of Escherichia coli K-12.

The final full paragraph of column 3 on page 1454 of Blattner et al. states, "The genome of E. coli, diagrammed in Fig. 1, consists of 4,639,221 bp of complex DNA." Consequently, Figure 1 on page 1465 of Blattner et al. illustrates an *in silico* map of the complete genome of E. coli.

The first full paragraph of column 1 on page 1454 of Blattner et al. describes the annotation process of identifying ORFs in genes constituting operons, regulatory sites, mobile genetic elements, and repetitive sequences in the genome, assigning and suggesting functions, and relating the E coli. sequence to other organisms. The second full paragraph of column 1 on page 1454 states:

> Functions of previously known E. coli proteins were collected from the GenProtEC and EcoCyc database. The function of new translated sequences was inputted from sequence similarity.

Consequently, functions are assigned to proteins by determining similarities (i.e. homologies) to proteins of known function.

The result of assigning functions to proteins is Table 4 on page 1459 of Blattner et al. wherein metabolic genes are classified as such in their specific metabolic classes listed in Table 4 of page 1459 of Blattner et al. One of the classes listed is nucleotide synthesis and metabolism.

The first full paragraph of column 2 on page 1454 of Blattner et al. describes the use of BLAST in assigning function to proteins.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the stoichiometric model of E. coli metabolism as taught by Pramanik et al. by use of the complete genome sequence of Blattner et al. wherein the motivation would have been that by knowledge of the full genome of E coli, not only can metabolism be further analyzed, but also knowledge of the entire sequence of E. coli enables global approaches to understanding biological function in living cells and has led to new ways of looking at the evolutionary history of bacteria [see first paragraph of introduction on page 1453].

Response to Arguments:

Applicant's arguments filed 24 march 2008 have been fully considered but they are not persuasive.

Applicant has several arguments regarding this rejection on pages 7-10 of the Remarks. Applicant's arguments are essentially that there is no motivation to combine the two references, there is no reasonable expectation of success in combining the references, and all of the limitations are not taught or suggested.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation is stated above as:

> It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the stoichiometric model of E. coli metabolism as taught by Pramanik et al. by use of the complete genome sequence of Blattner et al. **wherein the motivation would have been** that by knowledge of the full genome of E coli, not only can metabolism be further analyzed, but also knowledge of the entire sequence of E. coli enables global approaches to understanding biological function in living cells and has led to new ways of looking at the evolutionary history of bacteria [see first paragraph of introduction on page 1453].

Applicant additionally alleges that the combination of the references is not sufficient because Pramanik et al. allegedly "teach[es] away from using models that are

not produced from existing biochemical information." Applicant continues by citing page 4, paragraph one of the instant specification in support of this statement. It is noted that while applicant cites the specification and NOT Pramanik et al. for evidence of teaching away for the invention, the invention as CLAIMED uses "proteins of KNOWN function" (i.e. see line 7 of instant claim 49). Consequently, although applicant alleges that Pramanik et al. is useful for teaching models not produced from existing biochemical information, the invention as claimed, has a knowledge base of the metabolic process before the method of the claim is executed.

In response to applicant's argument that there is no reasonable expectation of success in combining Pramanik et al. with Blattner et al., the study of Pramanik et al. is a general study of biochemical processes and is applicable to such sequences and genomes indicated in Blattner et al. Consequently, there is a reasonable expectation of success in applying the general study of Pramanik et al. to the specific instance of Blattner et al.

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #2:

Claim 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pramanik et al. in view of Blattner et al. as applied to claims 49-52 and 56-60 above, and further in view of Xie et al. [TIBTECH, 1997, volume 15, pages 109-113].

Pramanik et al. and Blattner et al. make obvious a method of simulating a metabolic capability of an in silico strain of a microbe by simulating metabolism within E. coli, as discussed above.

Pramanik et al. and Blattner et al. do not teach calculation of uptake rates by measuring depletion of substrate from the growth media.

The study of Xie et al. studies integrated approaches to the design of media and feeding strategies for fed-batch cultures of animal cells.

Column 2 on page 109, lines 3-7 of Xie et al. states:

> Obviously, a high viable cell density maintained for a long time is required to maximize product concentration. However, this mainly depends upon the composition of the medium employed.

Consequently, the composition of the growth medium and its depletion over time affects the growth of the cells.

The motivation of the study of Xie et al. is that by knowing this fact, better compositions for culture media can be designed (i.e. see page 110 of Xie et al.)

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the metabolism studies of E. coli of Pramanik et al. in view of Blattner et al. by use of the nutrient depletion studies of Xie et al. wherein the motivation would have been by knowing how nutrients are depleted in order to facilitate cell growth, stronger media can be designed to enable better growth of the cells in the cellular media [see page 110, column 1-2 under “Motivation for medium design,” and “Design of culture environment.”] There would have been a reasonable expectation of success in applying the animal cell study of Xie et al. to the bacterial studies of

Pramanik et al. and Blattner et al. because when all cells are cultured, whether animal or bacterial, the cells need nutrients to survive, and as a result, all species of cells deplete their culture media of these nutrients.

Response to Arguments:

Applicant's arguments filed 24 March 2008 have been fully considered but they are not persuasive.

Applicant argues that the reference of Xie et al. does not cure the alleged deficiencies of the combination of Blattner et al. and Pramanik et al. For the reasons discussed above, the combination of Pramanik et al. and Blattner et al. is not deficient.

## *Conclusion*

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/RSN/
Russell S. Negin
14 June 2008

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631